Paper No. 20

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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Ex parte ALLEN E. GOODSHIP, PETER WALKER, DONAL S. McNALLY, TIMOTHY J. CHAMBERS, and JONATHAN GREEN

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Appeal No. 1997-2751
Application No. 08/159,096

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ON BRIEF

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Before WILLIAM F. SMITH, MILLS, and GRIMES, Administrative Patent Judges, GRIMES, Administrative Patent Judge.

## DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-14, all of the claims pending in the application. All of the claims are drawn to a method of treating bone fractures in mammals by administering one of a class of diphosphonate compounds.

The examiner relies on the following references:[1]

European Patent
Gall et al. (Gall) 0 252 505 Jan. 13, 1988

Henricson et al. (Henricson), "The Effect of Diphosphonates on Fracture Healing in Rats Stuidied with Monoclonal Antibodies," Calcified Tissue Int., Vol. 39 (Suppl.), page A74 (1986).

Kanis, "Treatment of Osteoporotic Fracture," The Lancet, pp. 27-33 (1984).

Fitton et al. (Fittion), "Pamidronate: A Review of its Pharmacological Properties and Therapeutic Efficacy in Resorptive Bone Disease," Drugs, Vol. 41, pp. 289-318 (1991).

Claims 1-14 stand rejected under 35 U.S.C. § 103 over the combination of Fitton, Gall, Kanis, and Henricson.

We reverse and enter a new ground of rejection under 37 CFR § 1.196(b).

## Background

As explained in Appellants' specification, bisphosphonate (aka diphosphonate) compounds are used clinically to inhibit excessive bone resorption associated with diseases such as osteoporosis and Paget's disease. Because bisphosphonates inhibit bone resorption, researchers in the prior art generally expressed an expectation that they would interfere with the normal fracture-healing process. Appellants allege that, contrary to these expectations, certain methanebisphosphonic acid derivatives actually aid in the healing of bone fractures. Appellants state that these compounds "promote a more rapid and stronger fracture healing." Specification, page 2.

[1] The Examiner in her Answer did not provide proper citations for the references by Fitton, Kanis, or Henricson. See MPEP § 707.05(e) (a correct citation to an article in a periodical "includes the author(s) and title of the article and the title, volume number, issue number, date and pages of the

## Discussion

The pending claims are drawn to a method of treating fractures in mammals by administering a methanebisphosphonic acid compound. The examiner rejected all of the claims as obvious over Fitton, Gall,[2] Kanis, and Henricson. According to the examiner, Fitton discloses the use of bisphosphonate in "bone fracture medications" and Gall teaches use of bisphosphonates when the process of bone formation and breakdown is disturbed. The examiner cited Kanis and Henricson as showing "the breadth and wealth of knowledge of diphosphonates in bone therapy." Examiner's Answer, page 3. The examiner concluded that any differences between the prior art and the claimed method amounted merely to optimizing parameters, and therefore the cited prior art would have made the obvious the claimed method.

Appellants argue that the references cited by the examiner do not support a prima facie case of obviousness, for several reasons. Appellants argue that resorptive bone disorders (e.g., osteoporosis) are caused by a mechanism that is completely different from bone fracture. Appellants also argue that treatments for the two types of disorders are also completely different, in that the systemic

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periodical."). Fortunately, Appellants in their Brief provided full citations to the references relied on by the Examiner, allowing us to discern the basis for the rejection.

[2] We note that the examiner relied on EP 252505 (Gall), which is in German, in her statement of the rejection but cited to a U.S. Patent when discussing what is disclosed by Gall. We assume the U.S. Patent cited is 4,942,157 (Gall), which Appellants indicate in their Brief corresponds to EP 252505. We also note that U.S. Patent 4,942,157 issued on July 17, 1990, making it prior art with respect to the instant claims under 35 U.S.C. § 102(b). We are baffled by the examiner's reliance on a reference in German when a corresponding English language reference was in the record. It should be obvious that when two equivalent references are available, one in English

inhibition of bone resorption that is the basis for treating resorptive bone disorders would not have been expected to aid fracture healing. Finally, Appellants assert that the Examiner misread the prior art to suggest that fracture healing and treatment of bone loss require the same type of treatment, and ignored teachings in the prior art that would have led a skilled artisan to expect that bisphosphonate compounds would likely have a deleterious effect on fracture healing.

"It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references." Pro-Mold & Tool Co. v. Great Lakes Plastics Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

> Although couched in terms of combining teachings found in the prior art, the same inquiry must be carried out in the context of a purported obvious "modification" of the prior art. The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification.

In re Fritch, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1783-84 (Fed. Cir. 1992). Here, the examiner has concluded that it would have been obvious to modify the prior art methods by administering bisphosphonate compounds, not to prevent future bone fractures, but to treat fractures after they occur.

Having carefully considered the evidence and reasoning presented by Appellants and the examiner, we find ourselves in agreement with Appellants

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and one not, the reference in English should be preferred.

that the cited prior art provides no "reason, suggestion, or motivation" to modify the prior art in such a way. Rather, the cited references suggest that bisphosphonates would have been expected to interfere with, not aid, the process of bone fracture healing. For example, Gall teaches use of bisphosphonates to treat a variety of diseases (e.g., osteoporosis and Paget's disease) but does not suggest that such compounds would be useful to treat a bone fracture. Similarly, Fitton teaches use of bisphosphonates to treat Paget's disease and thereby reduce the risk of bone fractures, but says nothing to suggest that the compounds would be useful to treat fractures after they occur. In fact, one of the references relied on by the examiner actually teaches away from the claimed method. Kanis states that inhibitors of bone resorption such as bisphosphonates may "increase the risk of microfracture or delay their repair and lead to skeletal failure . . ., by reducing the rate of remodeling of damaged bone, inhibiting callus formation, or both." Page 27.

Appellants in their Brief pointed out that the bisphosphonates pamidronate and etidronate have been reported in the scientific literature to inhibit fracture healing. Appellants cited, among others, the references in the record by Reid et al. and Finerman et al. as disclosing adverse effects of bisphosphonates on fracture healing. In response, the examiner stated that Appellants' reliance on Reid and Finerman was "not part of the original rejection and any response to it would be considered new grounds of argument." Examiner's Answer, page 4.

The examiner erred in not addressing the teachings of Reid and Finerman cited by Appellants. "If a prima facie case [of obviousness] is made in the first

instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed." In re Hedges, 783 F.2d 1038, 1039, 228 USPQ 685, 686 (Fed. Cir. 1986). The fact that the examiner did not rely on these references in her rejection does not make a response to their citation by Appellants a new ground of argument. On the contrary, the examiner is required to reweigh the merits of the entire rejection in view of whatever argument, prior art, or experimental evidence is presented by an applicant in rebuttal. See id.; see also In re Rinehart, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976) ("When prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over.").

New Ground of Rejection

Under the provisions of 37 CFR § 1.196(b), we make the following new ground of rejection: The specification is objected to, and claims 1-14 are rejected, under 35 U.S.C. § 112, first paragraph, because the specification does not enable a person of skill in the art to make and use the claimed invention. As evidence supporting our conclusion of non-enablement, we rely on the references of record by Alpar, Kanis, Reid, Finerman, Henricson, and Lenehan.

Appellants' specification accurately summarizes the expectation of those skilled in the art that bisphosphonate compounds would interfere with, not aid, the fracture healing process. See the Specification at page 1:

> As the compounds bind to bone mineral and inhibit bone resorption, there has been general concern that bisphosphonates could have a deleterious effect on callus formation and remodelling, which is an

> essential part of the fracture repair process. Kanis, for example, teaches in Lancet 1984, 27-33 that bisphosphonates, as inhibitors of bone resorption, may indeed halt skeletal losses but on the other hand delay the repair of microfractures by reducing the rate of remodelling of damaged bone and inhibiting callus formation. As another example, Reid et al. in Lancet 1988, 143-146 found that bisphosphonate treatment, in this particular case done with disodium pamidronate (= APD), caused a reduction in bone formation and a very low rate of bone turnover which raised the possibility of impaired microfracture repair. Furthermore, Alpar, in J. Clin. Hosp. Pharmacy 9 (1984) 341-344, expressed the view that the natural process of bone healing cannot be influenced by any drug.
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> Furthermore, one commercially available bisphosphonate, disodium etidronate, is even known to inhibit bone mineralization and to delay callus formation and fracture healing in man and animals at doses within the therapeutic range [see G.A.M. Finerman et al., Clin. Orthopaed. Rel. Res. 120 (1976) 115-124; L. Flora et al., Metabol. Bone Dis. Rel. Res. 4/5 (1981) 289-300].

The specification accurately summarizes the prior art. Alpar reviews the bone healing process and concludes that "[i]t appears that this natural process cannot be influenced by drugs." Page 343. Kanis states that inhibitors of bone resorption such as bisphosphonates may "increase the risk of microfracture or delay their repair and lead to skeletal failure . . ., by reducing the rate of remodeling of damaged bone, inhibiting callus formation, or both." Page 27. In addition, Reid states that administration of (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate causes a "very low rate of bone turnover," and "raises the possibility of impaired micro[]-fracture repair." Page 145.

Experimental evidence generated by Finerman, Henricson, and Lenehan confirmed these expectations. Finerman reported that withholding diphosphonate treatment in two patients allowed fracture healing to proceed.

Page 123, left-hand column. By contrast, a patient who was continued on diphosphonate therapy after fracture showed "no healing of the fracture . . . 6 months later." Id. When diphosphonate administration was discontinued, bone union promptly occurred. Id.

Similarly, Henricson found that in rats treated with aminopropane diphosphonate, bone fracture healing (in particular inductive callus and enchondral bone formation) occurred more slowly than in control animals. In addition, Lenehan found that administration of ethane-1-hydroxy-1,1-diphosphonate caused a dose-dependent inhibition of fracture healing in dogs (see the abstract). Lenehan also stated that the effects on humans would be expected to be similar because of the similarity in bone remodeling between humans and dogs (page 507).

Thus, the prior art in the record shows that those skilled in the art would have expected administration of diphosphonate compounds to inhibit, rather than aid, the healing of bone fractures. The evidence thus shows that those skilled in the art would have doubted the efficacy of the claimed method, based on the evidence available at the time of the invention.

The instant specification presents no evidence to show that this expectation was incorrect. In fact, the record contains no evidence showing that the compounds recited in the claims have any beneficial effect on fracture healing. The specification contains a single example, which appears to be prophetic. The example (pages 4-5 of the specification) is presented in the present tense, suggesting that the work described had not actually been carried

out. The example also does not specify what compound was administered, further suggesting that a completed experiment is not being reported.

Confusingly, however, the example then presents "results," suggesting that some work had been done. On close inspection, however, it is apparent that no actual results are presented. Again, specific results are not reported for a specific compound and the rate of bone mineralization is reported as "e.g. 76% greater in the treated group than the controls" (emphasis added). We therefore conclude that the "results" reported in the specification are no more than what the inventors hoped to achieve in an actual experiment. The manner in which the specification presents this example is confusing at best, and possibly misleading to the casual reader, but the example appears to be merely prophetic, rather than an actual working example.

We are aware of only one piece of evidence in the record that might be interpreted to support enablement of the instant claims. Lenehan shows that at one specific dosage, administration of ethane-1-hydroxy-1,1-diphosphonate caused some beneficial effect on fracture healing. See page 505, right-hand column ("Biomechanical evaluation of fracture sites in group 2 [0.1 mg/kg/day] revealed fracture-healing characteristics that exceeded those of controls."). However, this isolated result is not sufficient to outweigh the other record evidence indicating nonenablement, for two reasons. First, the compound administered by Lenehan, although a diphosphonate, is not within the scope of the instant claims. Second, Lenehan expressed surprise that any dosage of ethane-1-hydroxy-1,1-diphosphonate would benefit fracture healing. See page

505, right-hand column ("The reason for this finding is unknown, since mineralization rates are not increased nor has this dose level been previously shown to increase activation frequency or appositional rate."). Therefore, this finding would not have led those skilled in the art to expect similar results from treatment of fractures with other diphosphonates, such as those recited in the instant claims.

As stated in In re Wright, 999 F.2d. 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993):

> [w]hen rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. If the PTO meets this burden, the burden then shifts to the applicant to provide suitable proofs indicating that the specification is indeed enabling.

Factors that bear on whether claims are adequately enabled include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

After reviewing all of the evidence in the record in light of the Wands factors, we conclude that the specification does not enable practice of the full scope of the claimed invention without undue experimentation. In particular, we note that the invention is of a nature which contradicts accepted scientific

knowledge about the nature of fracture healing and the in vivo mechanism of action of diphosphonates; that is, those of skill in the art expected that diphosphonates would act to interfere with, rather than aid, fracture healing. In addition, the state of the prior art was such that those skilled in the art would not have considered practice of the claimed method to be feasible. Finally, the specification lacks any working examples or actual data to counter the art-based expectation that the claimed method simply would not work.

We conclude that the evidence of record provides sufficient basis for doubting the assertions in the specification as to the scope of enablement, and to shift the burden to Appellants "to provide suitable proofs indicating that the specification is indeed enabling." In re Wright, 999 F.2d at 1561, 27 USPQ2d at 1513.

Summary

We reverse the rejection of the claims as obvious over the references cited by the examiner but enter a new ground of rejection based on non-enablement.

This decision contains a new ground of rejection pursuant to 37 CFR § 1.196(b)(amended effective Dec. 1, 1997, by final rule notice, 62 Fed. Reg. 53,131, 53,197 (Oct. 10, 1997), 1203 Off. Gaz. Pat. & Trademark Office 63, 122 (Oct. 21, 1997)). 37 CFR § 1.196(b) provides that, "A new ground of rejection shall not be considered final for purposes of judicial review."

TIME PERIOD FOR RESPONSE

37 CFR § 1.196(b) also provides that the appellants, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of proceedings (§ 1.197(c)) as to the rejected claims:

> (1) Submit an appropriate amendment of the claims so rejected or a showing of facts relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the application will be remanded to the examiner. . . .
>
> (2) Request that the application be reheard under § 1.197(b) by the Board of Patent Appeals and Interferences upon the same record. . . .

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED
37 CFR ' 1.196(b)

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| WILLIAM F. SMITH<br>Administrative Patent Judge | ) |
| DEMETRA J. MILLS<br>Administrative Patent Judge | ) BOARD OF PATENT<br>) APPEALS AND<br>) INTERFERENCES |
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